09-24-01

JC05 Rec'd PCT/PTO 21 SEP 2001 PCT

JC962 U.S. PTO 09/21/01

FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: CWR 2 0265

U S APPLICATION NO (If known, see 37 CFR 1 5): 09/937227

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/07829	24 March 2000	24 March 1999

TITLE OF INVENTION: APPARATUS AND METHOD FOR DETERMINING MAGNETIC SUSCEPTIBILITY

APPLICANT(S) FOR DO/EO/US: Farrell, David, E., et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

"Express Mail" Mailing Label Number EL805266337B3

Date of Deposit Sept 21, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

R Stepka

(TYPED OR PRINTED NAME OF SENDER)

R Stepka

(SIGNATURE)

U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/937227	INTERNATIONAL APPLICATION NO PCT?US00/07829	ATTORNEY'S DOCKET NUMBER CWR 2 0265

21 ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
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Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	16 - 20 =	-0-	x **$18.00**	$	
Independent claims	3 - 3 =	-0-	x **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$ (345.00)	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$345.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 345.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 060308 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

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APPARATUS AND METHOD FOR DETERMINING MAGNETIC SUSCEPTIBILITY

Background of the Invention

This invention relates to an apparatus and method for high-sensitivity non-destructive evaluation of the magnetic susceptibility. The method utilizes a combination of components operating at a temperature - in the vicinity of 77 degrees Kelvin, the temperature of liquid nitrogen boiling under atmospheric pressure. The resulting device can measure the magnetic susceptibility in a wide variety of materials ranging from human tissue to industrial products. While the invention has a broad range of utility, its sensitivity and potential can be understood by considering the details of a specific practical application – the determination of the (in-vivo) magnetic susceptibility of the human liver.

The motivation for this application stems from the medical need for a device that measures body iron stores in an accurate, safe and non-invasive manner. Three recent developments have added to the urgency of this application: (i) the discovery of the gene responsible for most cases of hereditary hemochromatosis, (ii) the recent demonstration that transfusion therapy is an effective means of preventing stroke in patients with sickle cell disease, and (iii) the availability of new iron-chelating agents for the treatment of transfusional iron overload in patients with thalassemia major (Cooley's anemia), myelodysplasia and other forms of refractory anemia.

Being a transition metal, the iron atom can serve as a carrier for oxygen and electrons and as a catalyst for oxygenation, hydroxylation, and other critical metabolic processes. The very reactivity that is metabolically useful also makes iron potentially

hazardous. Ionic iron can participate in a number of reactions to produce free radical species, which can in turn damage cellular constituents. As a consequence, if too much iron accumulates (iron overload) and exceeds the body's capacity for safe transport and storage, iron toxicity can produce widespread organ damage and death.

Iron overload is caused by conditions that alter (hereditary hemochromatosis, refractory anemia with ineffective erythropoiesis) or bypass (transfusional iron overload) the normal control of body iron content by regulation of intestinal iron absorption. In all varieties of the disorder, the development and severity of organ damage is closely correlated with the magnitude of the body iron excess. Symptomatic patients may present with any of the characteristic manifestations of iron overload: liver disease with the eventual development of cirrhosis and hepatocellular carcinoma, diabetes mellitus, gonadal insufficiency and other endocrine disorders, arthropathy and increased skin pigmentation; iron-induced cardiomyopathy may be lethal.

All the existing methods for estimating body iron stores, indirect and direct, are subject to serious limitations. The many *indirect* measures of body iron status (e.g., plasma ferritin, plasma ferritin iron, transferrin and transferrin saturation, urinary iron excretion after injection of an iron chelator, erythrocyte protoporphyrin levels) have the advantage of ease and convenience, but clinical experience has shown that these indirect methods may often be misleading. All are subject to extraneous influences and lack specificity, sensitivity, or both. Equipment for magnetic resonance imaging has been widely available for many years, but no satisfactory quantitative procedure for iron estimation has been developed or clinically applied. Radioisotope methods remain research procedures. Diagnostic x ray spectrometry, a technique that can estimate

dermal iron content, does not provide a measure of total body iron load.

The available direct measures of body iron status do yield quantitative determinations of body or tissue iron stores, but have equally serious limitations. For example, tissue biopsy of the major iron storage sites, the liver and bone marrow, may provide either qualitative (histologic) or quantitative (chemical analysis) means of ascertaining iron status. While the technique provide the most quantitative direct measures of iron status generally available, its discomfort, and for liver biopsy, risk, limit their acceptability to patients and preclude their frequent use in serial observations

Thus, despite a pressing medical need, at present no satisfactory quantitative method for serial measurements of human iron stores is clinically available.

When placed in a steady applied magnetic field, all materials respond by creating a magnetic field of their own. The magnetic response of any particular material is controlled by the structure of the constituent atoms and molecules. The magnitude and direction of this response varies from material to material. In most human tissues (and bone) the induced field is weak and diametrically opposed to the applied field. By contrast, ferromagnetic materials (such as the common bar magnet) respond with an induced field as strong or even stronger than the applied field, and in the same direction. No known human tissues are ferromagnetic. Intermediate between the dia- and ferromagnetic extremes is the paramagnetic response of the iron in ferritin and hemosiderin. Their responses have a strength of about 10^{-4} of the applied field, and are in the same direction. This paramagnetic response is directly proportional to the number of iron atoms present in iron storage compounds. In a measurement of hepatic magnetic susceptibility in vivo, the opposing diamagnetic (tissue) and augmenting paramagnetic

(storage iron) responses are superimposed. By allowing for the small and nearly constant diamagnetic effect of the liver tissue, the observed resultant magnetic susceptibility may be used to determine the number of storage iron atoms present. The contributions of other paramagnetic materials (oxygen, deoxyhemoglobin, some trace metals) to the hepatic magnetic susceptibility are so small that magnetic measurements are highly specific for ferritin and hemosiderin iron.

The magnetic approach to the measurement of hepatic iron has been in (limited) use for about twenty years. The elements of a commercially available instrument are illustrated schematically in Figures 1(a) and (b). The susceptibility probe P contains two elements - a localized field source (current-carrying coils) to produce a magnetic field B, and a magnetic field detector. A subject S is placed directly below the probe, with the liver positioned in the region to which the field detector is maximally sensitive. The subject is then lowered away from the probe, as shown in Figures 1(a) and (b). Because of the localized character of the both the magnetic field and the response of the field detector, the field change observed, B, contains three principal contributions:

$$B = B_L + B_S + B_N \quad \ldots.(1)$$

where B_L, B_S, and B_N, are, respectively, the contributions from the liver, subcutaneous tissues and skin (and nearby tissues, including the lung), and instrumental noise. The latter is generally negligible, so that equation 1 reduces to:

$$B = B_L + B_S \quad \ldots.(2)$$

Consequently, the chief measurement uncertainty derives from the contribution made by the subcutaneous tissues, skin, and nearby organs, including the lung. In

principle, knowing the geometry and magnetic susceptibility of these regions, B_S may be calculated to any desired accuracy. In practice, obtaining the geometrical information alone would make the clinical procedure time-consuming and expensive.

To circumvent the geometrical problem, a differential measurement technique is employed. This depends on the circumstance that, with the important exceptions of iron-loaded liver and air-filled lungs, the susceptibility of most biological material is close to that of water. In a *differential* measurement, the patient is lowered, as described above, but the body directly under the detector is replaced by water form a water supply rather than air. using a water bellows arrangement like that shown schematically in Figures 2(a) and (b). When the body is lowered in air, the susceptibility of the various regions under the detector are measured. By contrast, when the measurement is made differentially, the detector's response is proportional to the *difference* in susceptibility between the organs and that of water. Since the tissues overlying the liver have a magnetic susceptibility very close to that of water, the water bellows method largely cancels out the contribution of the tissues overlying the liver. The lungs (and possibly gas-filled intestines) can have a susceptibility significantly different from that of water but are not directly under the detector, so their contribution is small.

All previous quantitative hepatic iron instrumentation has exploited the phenomenon of low-T_C superconductivity. The defining property of a superconductor is the loss of electrical resistance below a certain temperature, called the transition temperature, or T_C. All superconducting materials known prior to 1986 had transition temperatures not far above absolute zero and so are called "low- T_c" superconductors. A bath of liquid helium (at a temperature of 4.2K) is required to keep the temperature of such materials below T_c. In 1986, high- T_c materials with transition temperatures well above that of liquid nitrogen (77K) were discovered, very much simplifying the refrigeration problem.

The observed field change, B, in Equation 1 above is very small – typically less than

one millionth of the earth's magnetic field. Furthermore, it occurs in the presence of a steady field that is applied to the region of the liver, which can itself be a thousand million times larger than B. These conditions create a *dual* requirement for a liver-iron field detector, namely, extreme sensitivity *and* the stability to resolve a tiny field change in the presence of a large background . These requirements can be satisfied *only* by superconducting detectors, embodied as SQUIDS (Superconducting Quantum Interference Devices) and flux-transformers. The operation of these devices relies on a quantum-mechanical property only possessed by superconductors and termed flux-quantization. As a consequence, SQUID detectors have a *stability* that is possessed by no other field-sensing device.

To understand the origin of this stability, consider the situation shown schematically in Figure 3. A superconducting coil C (called a flux transformer) is cooled down in a field, B, produced by a steady localized magnetic field. Because no current is induced in the transformer when it enters the superconducting state, the magnetic flux through the loop is "trapped" by the flux quantization constraint. Furthermore, as long as the material remains superconducting, this flux can never change from the initial value.

If the total field in the vicinity of loop L1 changes by a small amount, ΔB (due, for example, to the introduction of the body of a patient), then a current I must appear in the transformer so as to keep the *total* flux trapped at its initial value. The flux generated by this current is equal but *opposite* to the flux generated by the change in the magnetic field, the net flux change being zero. The flux produced by the current in loop L2 can be detected by a SQUID, located in a field-free (shielded) location. The function of the flux transformer is therefore to take a flux *change* and transport it to a field-free location, where it can be measured by the SQUID. The critical point is that a flux transformer responds with a current proportional to the *change* in flux in a detector coil, not the *total* flux. In device terms, the superconducting property of flux quantization ensures that the

field measurement is *intrinsically* differential. The field change due to a normal complement of iron is extremely small (~a part in a billion of the applied field), so a powerful differential technique is required for any practical liver-iron instrument.

Over the last two decades, low-T_c SQUID bio-suceptometers have been used in investigative studies with hundreds of patients with all forms of iron overload. As a research tool, the devices have provided important new data. At present, however, there are only two susceptometers in clinical use in the world. The main problems with the existing instrumentation are the expense and complexity associated with the use of liquid helium, together with the limited accuracy due to the inadequate rejection of the signal from contiguous organs.

As mentioned previously, superconductors having high critical temperatures, referred to as "high-T_c" superconductors, were discovered in 1986. These materials display the phenomenon of superconductivity at temperatures above that of liquid nitrogen (77K), substantially higher than the temperature of liquid helium (4.2K). Liquid nitrogen temperatures can be established and maintained with much greater ease than those of liquid helium. However, two practical difficulties have so far prevented the widespread application of high-T_c materials. First, because of limitations which appear to be intrinsic to their novel form of superconductivity, superconducting coils with high-T_c material cannot provide magnetic fields of sufficient strength or stability for susceptometry applications. Furthermore, no flexible high-T_c wire has yet been produced, preventing the production of a suitable flux transformer. Because of these difficulties, high-T_c superconductors have never previously been used for magnetic susceptibility instrumentation.

Because it provides a non-invasive (and therefore non-destructive) measure of a fundamental physical quantity, it is clear that magnetic susceptibility determinations of the sort discussed above are of significant potential value in a wide variety of industrial

and medical situations. However, for all such applications, the prior (low-T_c) technology has the limitations discussed and its high-T_c variant has remained unrealized.

The present invention introduces a method and apparatus for determining the magnetic susceptibility in bodies that exploits the advantages of high-T_c superconductivity to overcome the specific shortcomings of prior devices.

Summary of the Invention

An apparatus and method for determining magnetic susceptibility in an object are provided.

In one aspect of the invention, the apparatus comprises a permanent magnet, a SQUID (superconducting quantum interference device) and a flux transformer comprising superconducting material disposed on a flexible metallic substrate, all three elements being maintained at a temperature of ~77K.

In another aspect of the invention, the method comprises applying a magnetic field to a material of interest using a permanent magnet, moving the object into the zone, inducing a current in a flexible superconducting flux transformer based on a change in the magnetic field when the object is moved in the zone, detecting the induced current in the transformer by a superconducting quantum interference device and calculating the magnetic susceptibility of the object based on the detected induced current.

Practical details of a specific example of the present invention are given in the description provided below. It should be understood, however, that this specific example, while indicating preferred embodiments of the invention, is given by way of illustration only. Various changes and modifications within the spirit and scope of the invention will be apparent to those skilled in the art.

Description of the Drawings

The present invention exists in the construction, arrangement and/or combination, of the various parts and steps, whereby the objects contemplated are attained and

hereinafter more fully set forth and illustrated in the accompanying drawings in which:

Figures 1(a) and (b) illustrate the elements of susceptometric measurement of hepatic storage iron. The body is positioned so that the liver lies directly beneath the susceptibility probe, then lowered and the field change measured by the field detector.

Figures 2(a) and (b) illustrate a *differential* measurement of hepatic storage iron that is made by lowering the subject from the initial position and replacing the body by water.

Figure 3 illustrates the principles of the superconducting flux transformer. B is the applied field and I is the current induced by a change in the field, ΔB.

Figures 4(a) and (b) are a graphic representation of a six-channel high-T_c susceptometer probe. Four of these channels are devoted to first-order high-T_c gradiometers, as shown to the left. One of these gradiometers is for the susceptibility determination ; the signals from the other three are used to cancel the contribution of the skin overlay. The other two SQUID channels are for electronic cancellation of the ambient hospital noise.

Figure 5 is a schematic illustration of the entire system for a high-T_c bio-susceptometer probe of Figures 4(a) and (b).

Figure 6 is a flowchart illustrating the method according to the present invention.

Figure 7 is a graphic comparison chart showing the (cryogenically limited) flux responses of low and high-T_c technologies. The response ratio between two different coils (defined in the text) is plotted as a function of distance of the torso beneath them. The results indicate the improved resolution that will be obtained with high-T_c technologies.

Figure 8 is a graphic illustration of a device for measurement of weak magnetic susceptibilities of liquid solutions. The field changes produced by approaching then withdrawing (room temperature) samples in glass vials were detected by a 1cm wide detector loop of high-T_c material, configured from $Y_1Ba_2Cu_3O_7$ deposited on flexible

tape, as described below. The field change is proportional to the liquid's magnetic susceptibility. Note the opposite sign of the changes associated with water (diamagnetic) and ferrous sulfate solution (paramagnetic). The susceptibility values indicated were obtained using a low-T_c bisosusceptometer. The values obtained from the high-T_c version agree with these to within the measurement uncertainty.

Description of the Preferred Embodiments

The present invention incorporates a variety of design innovations applicable to the exemplary bio-susceptometer described herein and other contemplated embodiments of the invention; however, three preferred innovations over known devices are described as follows. First, the superconducting magnet is replaced by a permanent (NdBFe) magnet. Second, the low-Tc (wire) flux transformer is replaced by a (flexible) superconducting film of the high-Tc superconductor $Y_1Ba_2Cu_3O_7$. Third, the low-T_c SQUID is replaced by a high-T_c SQUID, also based on $Y_1Ba_2Cu_3O_7$. As a result of combining these three innovations, which will be more particularly described below, the system functions at approximately 77K (e.g. liquid nitrogen temperature), in contrast to the temperature requirement (approximately 4.2K -- e.g. liquid helium temperature) for all previous SQUID based bio-susceptometers.

Referring now to Figures 4(a) through 8 wherein the showings are for purposes of illustrating the preferred embodiments of the invention and not for purposes of limiting same, Figures 4(a)-(b) and 5 show an overall view of the apparatus of the preferred embodiment of the invention. As shown in Figure 4(a), an apparatus, or probe, 10 comprises a permanent magnet 12, superconducting quantum interference devices (SQUIDs) 14, and flux transformers 16 coupling the susceptibility signal to the SQUIDs 14. The connection is also illustrated in the box B wherein the operational coupling of the SQUIDs 14 and magnet 12 is representatively shown. Also provided are shields 18

and cables 20 to connect the apparatus 10 to a suitable data processing, or computer, system, as will be more particularly described in connection with Figure 5.

The (magnetic) shields 18 are preferably constructed from mu-metal. Their role is to shield the SQUIDS from extraneous laboratory magnetic fields.

Figure 4(b) shows the flux transformers 16. Specifically, it should be recognized that each flux transformer 16 has incorporated thereon patterns 22. These patterns comprise the gradiometer superconducting transformers embodied in the present invention.

More particularly, referring back now to the components of Figure 4(a), the permanent magnet 12 is preferably constructed of NdBFe (Neodymium boron iron) material. As discussed below, a permanent magnet of this preferred form provides an extremely stable magnetic field at liquid nitrogen temperatures. This feature of the present invention alone facilitates a significant improvement over prior known systems. Specifically, use of the preferred permanent magnet allows for replacement of the superconducting coil employed in the instruments of the prior art.

The field stability of NdBFe (Neodynium, Boron, Iron) was measured, using a high-T_c SQUID and flux transformer in a magnetometer configuration. Over a clinical measurement period (10 sec), the field drift at T = 77K was found to be less than a part in 10^9. Typical permanent magnet MRI require special precautions to stabilize the temperature of the room and/or the magnet. In sharp contrast, the stability of NdBFe at liquid nitrogen temperatures is sufficiently good that neither precaution is required.

Aside from its stability, there are five other technical characteristics which make a NdBFe permanent magnet a preferred field source for susceptometry of the sort under consideration:

- Field Strength: Typical field strengths are ~0.5Tesla. The actual field applied to the liver is at least ten times larger than in the previous low-T_c instruments,

increasing the signal to noise ratio by the same factor.

- Incremental susceptibility. For the small field changes of interest here, the *change* in the magnetization (of the magnet material itself), ΔM, produced by a small change in the magnetic intensity, ΔH is directly proportional to ΔH. The ratio of these quantities is called the incremental susceptibility, χ_{in}. For soft iron, the incremental susceptibility can be extremely large ($\chi_{in} \sim 10^3$ in SI units), very much complicating both calculations and the response of gradiometers in proximity to the material. For NdBFe, by contrast, the magnetic moment is insensitive to small changes in the applied field. This translates into an extremely small incremental susceptibility ($\chi_{in} < 10^{-2}$). This is an important technical advantage. It means that the approximation $\chi_{in} = 0$ is realistic for the modeling calculations and that no complications for gradiometer construction will arise.
- Hysterisis. For the small changes in field that are involved in our measurements, there is no measurable hysterisis in the magnetic response of NdBFe.
- Configuration. The material can be readily formed into a wide variety of shapes and sizes. Therefore, the magnet can be readily adapted to the configuration of a variety of target objects.
- Simplicity. No ancillary power supply is required to charge the magnet.

With continuing reference to Figure 4(a), as noted, the SQUIDs 14 are coupled to the region of interest 12 by flux transformers 16. Preferably, the SQUIDs are high-T_c SQUIDs and are inductively coupled to the flux transformer in order to measure the current that is induced in the flux transformer during use.

More specifically, high-performance thin-film SQUIDS fabricated from $Y_1Ba_2Cu_3O_7$ are preferable (preferably having a noise level at 1Hz of $\sim 10^{-13}T/\sqrt{Hz}$). There are preferably six SQUIDS employed in the illustrated design. Four of these monitor the signal from special flux transformers discussed above. Two are used to

cancel both field and gradient environmental noise. The number of SQUIDS, of course, may vary, depending on the particular application.

As to flux transformers in general, until recently, only non-flexible *planar* flux transformers were constructed using single-crystal thin-film $Y_1Ba_2Cu_3O_7$ technology. However, shielding the bio-susceptometer detection system from ambient field variations is most easily accomplished using axial *gradiometer* configurations. No such configuration can be configured from a pick-up coil confined to plane.

A process has recently been developed for depositing high quality one micron films of $Y_1Ba_2Cu_3O_7$ onto flexible metallic tape. The technique uses an intermediate buffer-layer that is oriented using ion-beam assisted deposition (IBAD) technology. It has been established that this tape can be given a radius of curvature of ~1cm without degrading the superconducting properties of the $Y_1Ba_2Cu_3O_7$ layer. The superconducting flux transformers 16 are produced from this material by etching away the undesired areas. As shown in Figure 4(b), the preferred design employs four first-order gradiometer flux transformers of different sizes to effectively image different depths of the body, allowing the instrument to cancel variations arising from contiguous organs.

As noted above, it is to be appreciated that the cables 20 connect the apparatus 10 to a suitable data processing system that includes custom control and acquisition software so that the information detected by the system can be appropriately manipulated and used. This system will be described with reference to Figure 5 wherein the clinical system embodies a number of features that are standard to all clinical bio-susceptometers and will be familiar to those versed in the art. These include: Dewar, bed, gantry, locator loop, water bag, and computer analysis system. Of course, it is recognized that suitable changes to the system could be made that should be apparent to those skilled in the art.

In Figure 5, the apparatus 10 is housed and supported within a dewar 50 that is filled with liquid nitrogen 52. A cryo-cooler system could also be employed to establish the

required temperature of 77K. Preferably, in the case of a liquid nitrogen environment, the dewar 50 is constructed from G-10 fiberglass; however, any suitable dewar vessel could be used. It is to be appreciated that the SQUIDs 14 are positioned inside the dewar and operatively connected to SQUID controllers 54, preferably through cables 20 and junctions 56. The controllers 54 are in communication with a processing system 58 that includes an analog & digital input/output device 60, a computer 62, and a storage 64 that contains custom software. The processing system 58 is also operatively connected to an operator remote control and display 66 that is linked to a fill/empty solenoid 68. The solenoid 68 is connected with room vent 70, a vacuum 72 and a reservoir 74 that serves a bellows 76. The bellows 76 provides a physical interface between the apparatus 10 and a subject 78 having a liver 80 that is under evaluation by the system of the present invention.

It is to be appreciated that the subject 78 is positioned on a pad 82 of a movable table 84. The movable table 84 is linked to a position transducer 86 which is in turn connected to a position transducer interface 88. Of course, the interface 88 operates between the transducer 86 and the processing system 58. The movable table 84 is also linked to a vertical motion drive and controller 90 that receives signals from a motion controller interface 92. The interface 92 receives signals from the operator remote control and display 66 and the transducer 88.

A gantry 94 is shown which supports the dewar 50. In addition, a lock-in amplifier 96 is operatively connected between a SQUID controller 54, the processing system 58 and the subject 78.

In operation, referring now to Figure 6, the device 10 (capable of taking many suitable forms in a variety of operational environments, e.g. gantry arrangements such as that of Figure 5), can be used to accomplish the method 300. As shown, a magnetic field is applied to a zone where the measurement is to be taken by the permanent magnet

12 of the device 10 (step 310). An object is then moved into the zone (step 320). In the arrangement of Figure 5, the movable table 84 is moved toward the apparatus 10 until the bellows 76 is in contact with the subject 78 at a suitable location. It will be appreciated by those skilled in the art that the components illustrated (e.g. transducer 86, drive and controller 90 and processing system 58) operate in combination within the system to facilitate the movement of the table 84. Of course, in the case of smaller more portable versions of the invention, the device can be moved toward the object. The important feature of this step is that relative movement is accomplished between the device and the object.

Further movement of the object in the zone (e.g. away from the device 10 or toward the device 10) induces a current in the flux transformer 16 of the device 10 that is monitored by the SQUID system. As a result, the current is detected (step 330). The magnetic susceptibility can then be calculated based on the induced current that is detected (step 340). Again, those skilled in the art will appreciate that the illustrated components operate in combination to accomplish the task of determining magnetic susceptibility. For example, the data obtained through use of the SQUIDs 14 allows the custom susceptometer software in storage 64 to determine the susceptibility by manipulating the well-known principles described herein. The software enhances the analysis by preferably incorporating, for example, mathematical models, algorithms, regression analysis and knowledge obtained clinically of susceptibility variations. The function of the software is to reduce uncertainty in the analysis of liver iron, for example.

As is apparent from the above description of the invention, in addition to greatly widening the scope of clinical bio-susceptometry, the new design will also reduce the uncertainty of liver-iron determinations. For a localized field source, the sensitivity of a circular detector coil is mainly confined to a region directly beneath the coil with a spatial extent on the order of a coil diameter. By exploiting the ability of different sized

coil systems to "image" different regions of the body, including those contiguous with the liver (skin overlay and lungs), it will be possible to estimate their susceptibility. Previous efforts along these lines with low- T_c instrumentation have been hindered by the practical constraints imposed by liquid helium cryogenics. To provide a reasonable hold-time (~1 week) between transfers of liquid helium, a relatively large dewar (~25 liters) must be used. The closest that a detection coil of suitable size can conveniently be brought to the body is then in excess of 1cm. This distance makes it difficult to distinguish the magnetic contributions of hepatic tissue and the overlying subcutaneous tissues, muscle and bone. In addition, because of the technical difficulties problems encountered with different coil arrangements, the only geometry fabricated to date has been a planar circle. Taken together, these practical constraints have greatly limited the imaging capabilities of low- T_c instruments.

The present invention utilizes the preferred $Y_1Ba_2Cu_3O_7$ high- T_c detector "coil", and this can be configured into a wide variety of different shapes and sizes. With existing liquid nitrogen (and cryo-cooler) technology, such coils can be brought to within one or two millimeters of the body surface. The closer approach to the body that is possible with high-T_c coils greatly enhances their ability to "image" different regions of the body. The advantages are made explicit in Figure 7. A SQUID detection system responds to the magnetic flux through a detection coil, that is, the normal component of the magnetic field integrated over the area of the coil. Suppose $\phi_d(x)$ is the flux change measured in the coil when the body of the patient is lowered a distance x from its initial position, a distance x_0, beneath the coil. In principle, information about the susceptibility of the body as a function of depth can be derived from *differences* between the ϕ (x) of a set of coils of different diameter. Taking a specific example, suppose the body has a uniform magnetic susceptibility and that $\phi_6(x)$ and $\phi_1(x)$ are the fluxes detected by coils of diameter 6 cm and 1 cm, respectively, the field source being taken as a single coil of

diameter 6 cm. If $x_0 >> 6$ cm, then the ratio $\phi_6(x)/\phi_1(x)$, is *independent* of x, the situation indicated by the line labeled "no imaging capability" in Figure 7. (The ratio has been normalized so that $\phi_6(x)/\phi_1(x)$ tends to unity as x tends to zero). The conclusion just stated is essentially independent of body geometry. (For these calculations, the body was modeled as a cylinder of diameter and length both equal to 15 cm, the cylinder axis being co-axial with the coils.) As is evident, for large initial separations, there is no distinction between $\phi_6(x)$ and $\phi_1(x)$, and therefore *no* imaging capability. By contrast, as x_0 is reduced, the response ratio, $\phi_6(x)/\phi_1(x)$ departs strongly from unity. Results are shown in Figure 7 for separations typical of a low-T_C ($x_0 = 2.0$ cm) and a high- T_c ($x_0 =$ 0.3 cm) instrument, indicating that depth imaging will be significantly improved in the latter case. These results were obtained using the flux integral method that will be familiar to those skilled in the art. In a similar manner, the high-T_c coil separation also exhibits much better lateral imaging - the capability required to distinguish the liver susceptibility signal from that of the adjacent lungs. These advantages in imaging capability should allow magnetic measurements of hepatic storage iron *in vivo* to approach ~1 μmole Fe per gram liver, wet weight.

Referring more specifically now to Figure 8, the device 10 of Figures 4(a)-5 has been tested and shown to be practical. The device 110 is positioned within a testing apparatus 210 which comprises a polystyrene dewar vessel 212 that contains liquid nitrogen 214. The device 110 is positioned to be immersed in the liquid nitrogen in close proximity to inner surface 216 corresponding to aperture 218 in the vessel 212. A liquid sample stored in a glass vial 220 is brought in close proximity to the device 110 along the direction of the arrow 222. The liquids used for testing at room temperature were water having a diamagnetic susceptibility of -9×10^{-6} SI, and a magnetic salt solution. having a paramagnetic susceptibility of $+7 \times 10^{-5}$ SI. These samples were pulled back and forward along the direction indicated by the arrow 222.

The (magnetometer) flux transformer was fabricated from a 10x1cm section of $Y_1Ba_2Cu_3O_7$ tape, by masking and etching away the undesired material. A liquid nitrogen container was fabricated by gluing together pieces of 2.5 cm thick polystyrene. The thickness of this material was reduced to ~2mm in the vicinity of the detector coil. In a 1Hz bandwidth, the rms environmental magnetic noise as measured by the magnetometer was $\sim 10^{-9}$ T. Even without the benefits of gradiometer noise rejection, the susceptibility signals from the liquid vials at room temperature was easily detected. As noted above, these vials were lowered toward the detector in the direction of arrow 222, then removed, and the resulting field changes recorded using the SQUID. The ratio of the magnitude of the susceptibilities of the same samples was measured with a low-T_c liver-iron instrument and found to be 8:1, water being diamagnetic and the ferrous sulfate solution paramagnetic. Within the experimental uncertainty, the ratio of the observed field changes agreed with the measured susceptibility ratio.

The SQUID and flux transformer were thermally cycled to liquid nitrogen temperatures and back over a dozen times during the course of these measurement. In the past, deleterious changes on thermal cycling have presented a serious problem for high-T_c materials. Neither the SQUID nor the transformer exhibited any cycling degradation.

The results presented above establish the practical validity of a novel and powerful approach to bio-susceptometry. In particular, they establish that:

- A *flexible* high-T_c film can readily be configured into a superconducting transformer that exhibits the crucial property of flux-locking at liquid nitrogen temperatures. Furthermore, this property is retained in an applied magnetic field of 0.5T. Because of these two features, the transformer can be configured to conform to a variety of target objects.

- In view of its field strength, extremely small incremental susceptibility, and field stability at liquid nitrogen temperatures, commercially available NdBFe material provides

an ideal field source for bio-susceptometry.

- The high-T_c SQUID/transformer combination exhibits no degradation on thermal recycling.

The above description only provides a disclosure of the particular embodiments of the invention and is not intended for the purpose of limiting the same thereto. As such, the invention is not limited only to the above described embodiments, it is recognized that one skilled in the art could conceive alternative embodiments that fall within the scope of the invention.

What is claimed is:

1. An apparatus for determining magnetic susceptibility in an object, the temperatures being maintained at approximately 77K, the apparatus comprising:

a permanent magnet;

a superconducting quantum interference device constructed from material having a critical temperature above 77K;

a flexible superconducting flux transformer that couples the susceptibility signal to the superconducting quantum interference device, the transformer comprising superconducting material disposed on a flexible metallic substrate.

2. The apparatus as set forth in claim 1 wherein the permanent magnet is formed of neodymium (Nd), boron (B) and iron (Fe).

3. The apparatus as set forth in claim 1 wherein the flexible superconducting flux transformer comprises a nickel based substrate having disposed thereon a layer of yttria-stabilized zirconia and a thick film of epitaxial yttrium barium copper oxide.

4. The apparatus as set forth in claim 1 wherein the object is the (in-vivo) human liver.

5. The apparatus as set forth in claim 1 wherein the object is (in-vivo) human bone.

6. An apparatus for the measurement of the magnetic susceptibility of an object, the apparatus comprising:

at least one magnetic field source operable to produce a stable magnetic field at

liquid nitrogen temperatures;

at least one superconducting flux transformer formed from $Y_1Ba_2Cu_3O_7$ and having a first loop or coil encircling and a first area immersed in the magnetic field, a second loop or coil encircling a second area and a connection between the first loop or coil and the second loop or coil;

at least one high T_c superconducting quantum interference device, in close proximity, at least in part, to the second loop or coil of the superconducting flux transformer, the superconducting quantum interference device measuring the effect of the addition of flux from other magnetic fields introduced through the first loop or coil.

7. The apparatus of claim 6 wherein the magnetic field source is a permanent magnet.

8. The apparatus of claim 7 wherein the permanent magnet is made of neodymium boron ferrite.

9. The apparatus of claim 6 wherein the at least one superconducting quantum interference device is inductively coupled to the flux transformer and measures current that is induced in the flux transformer.

10. The apparatus of claim 6 wherein the at least one superconducting flux transformer is flexible.

11. The apparatus of claim 6 further comprising:

a data processing system;

at least one superconducting quantum interference device controller;

at least one cable connecting the at least one superconducting quantum interference device to the at least one superconducting quantum interference device controller;

at least one cable connecting the at least one superconducting quantum interference device controller to the data processing system;

data acquisition software run on the data processing system;

system control software run on the data processing system;

data analysis software run on the data processing system.

a housing enclosing the at least one magnetic field source, the at least one superconducting flux transformer, and the at least one superconducting quantum interference device;

a gantry supporting the housing;

a support surface for supporting the object in proximity to the housing; and,

an interface device between the housing and the object.

12. The apparatus of claim 11 wherein the gantry movably supports the housing relative to the support surface.

13. The apparatus of claim 11 wherein the support surface movably supports the object relative to the housing.

14. The apparatus of claim 11 wherein the housing further houses a refrigerant.

15. The apparatus of claim 14 wherein the refrigerant is liquid nitrogen.

16. A method for determining magnetic susceptibility in an object, the method

comprising steps of:

applying a magnetic field to a zone using a permanent magnet;

moving the object into the zone;

inducing a current in a flexible superconducting flux transformer based on a change in the magnetic field when the object is moved into the zone;

detecting the induced current in the transformer by a superconducting quantum interference device that has a high critical temperature; and

calculating the magnetic susceptibility of the object based on the detected induced current.

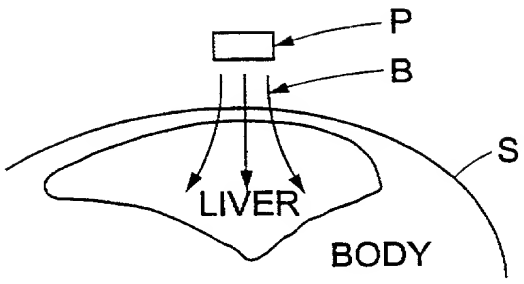


FIG. 1(a)

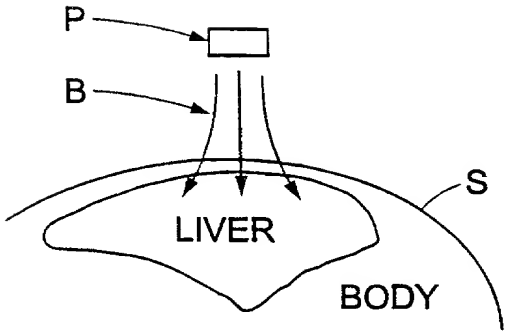


FIG. 1(b)

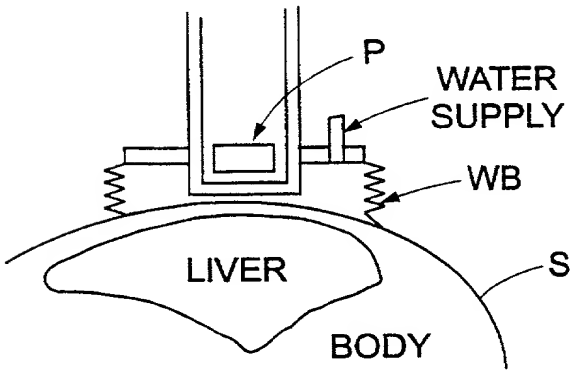


FIG. 2(a)

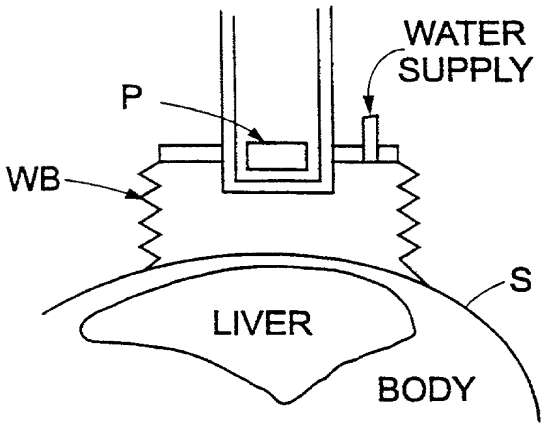


FIG. 2(b)

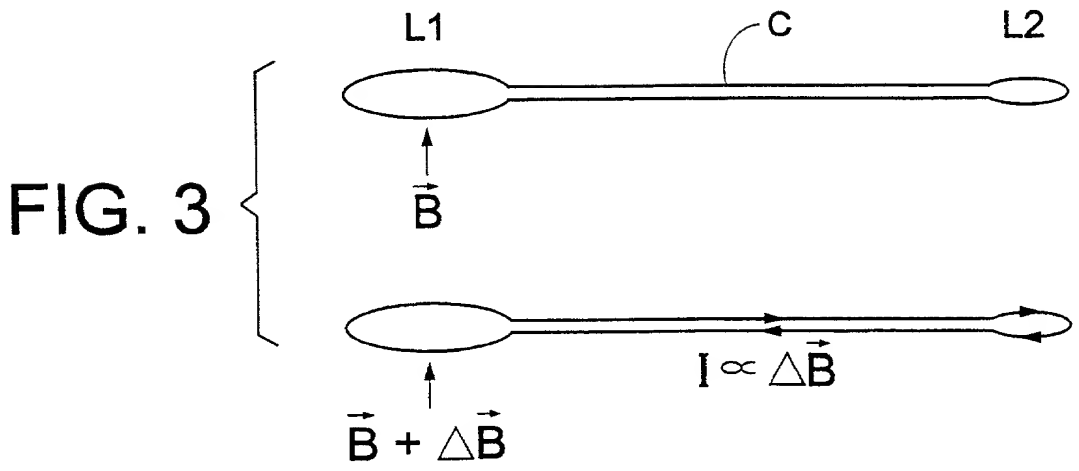


FIG. 3

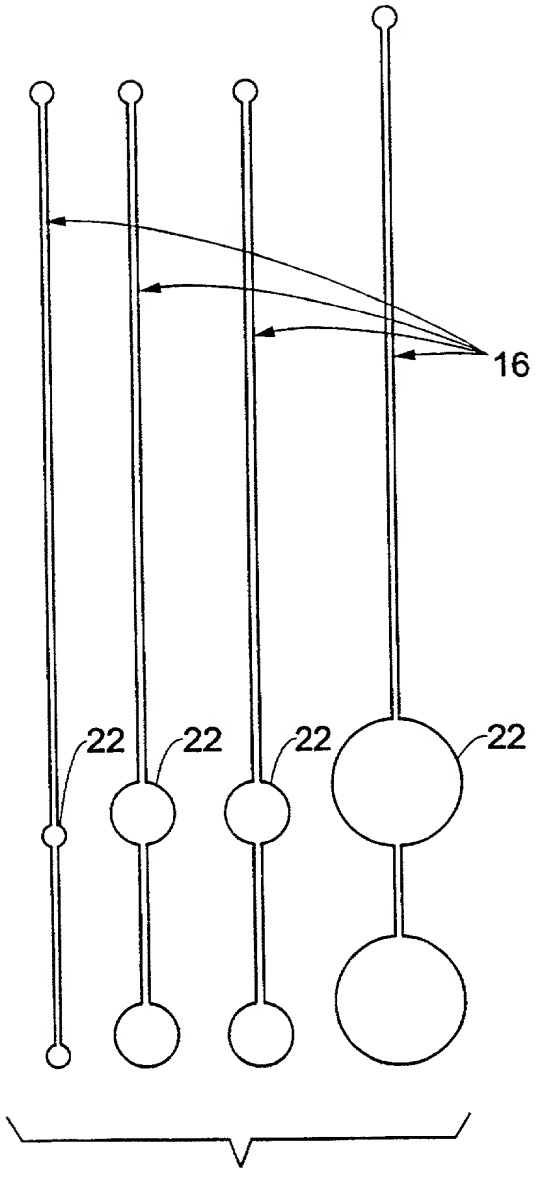


FIG. 4(b)

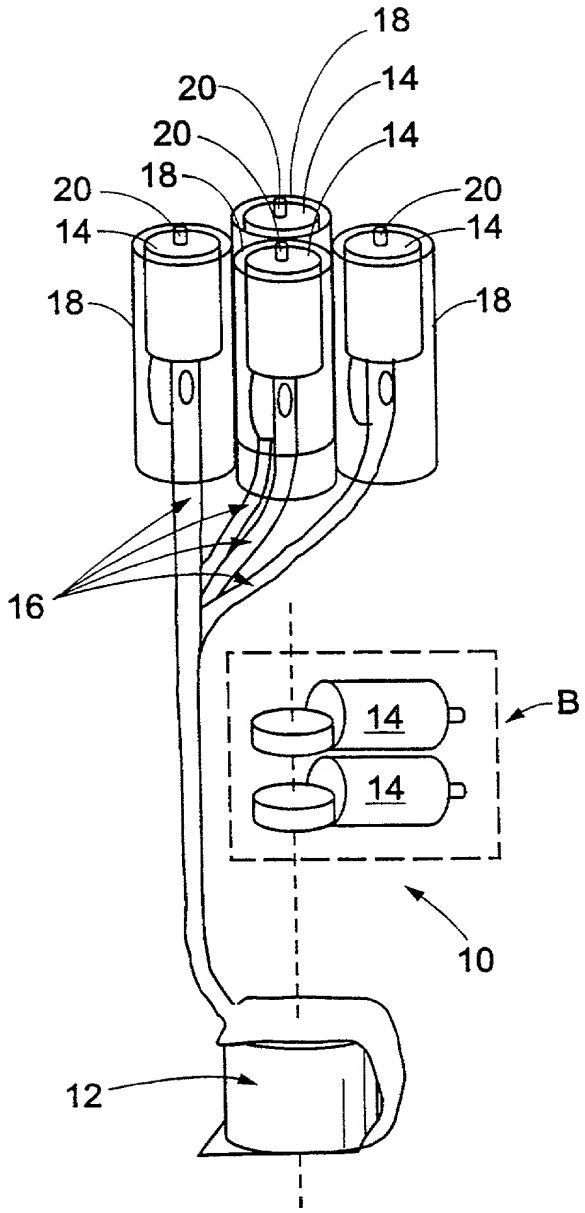


FIG. 4(a)

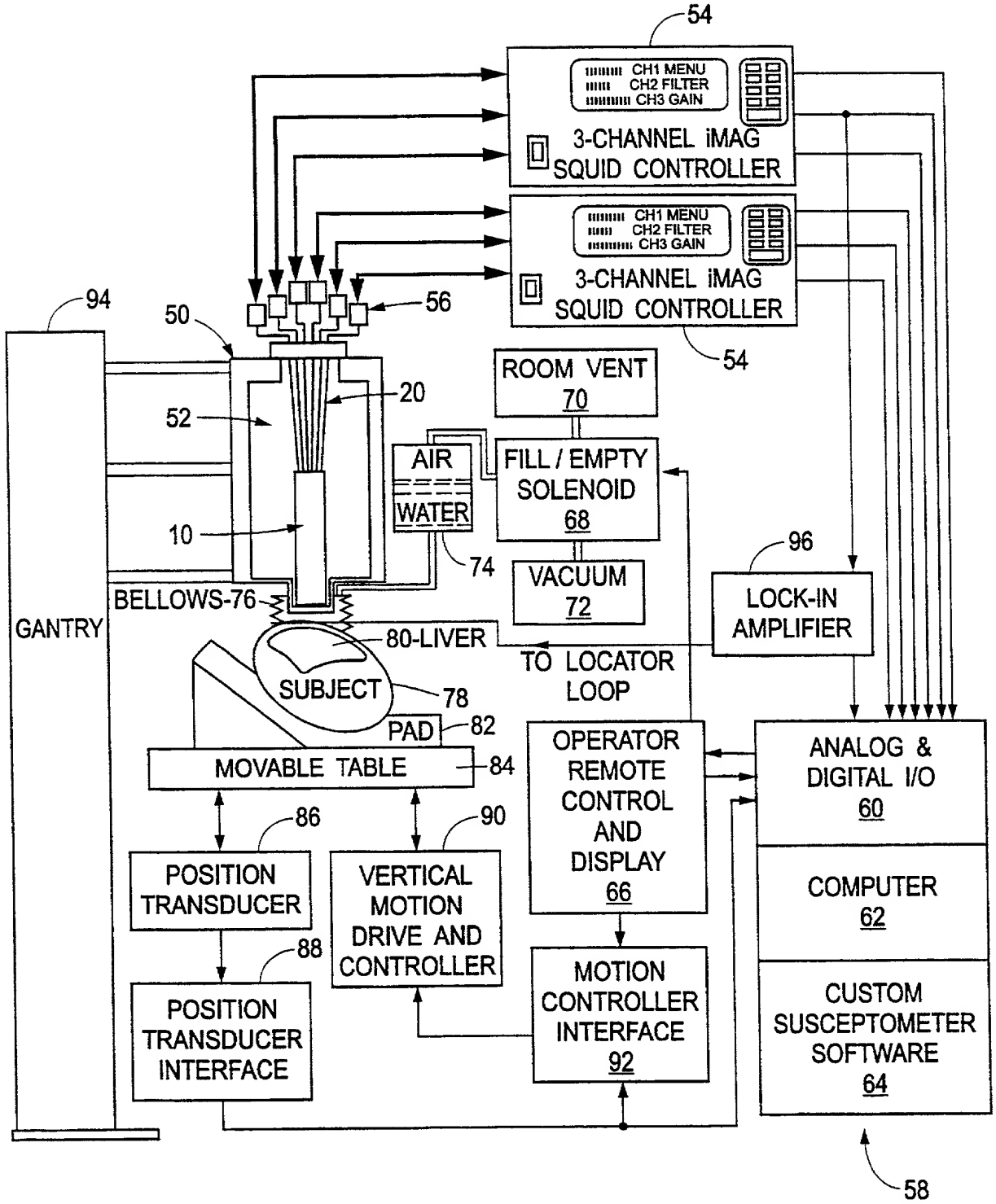

54
CH1 MENU
CH2 FILTER
CH3 GAIN
3-CHANNEL iMAG SQUID CONTROLLER
CH1 MENU
CH2 FILTER
CH3 GAIN
3-CHANNEL iMAG SQUID CONTROLLER
54
94
50
56
52
20
10
ROOM VENT 70
AIR
WATER
FILL / EMPTY SOLENOID 68
74
VACUUM 72
96
LOCK-IN AMPLIFIER
BELLOWS-76
GANTRY
80-LIVER
TO LOCATOR LOOP
SUBJECT
78
PAD
82
MOVABLE TABLE
84
OPERATOR REMOTE CONTROL AND DISPLAY 66
ANALOG & DIGITAL I/O 60
COMPUTER 62
CUSTOM SUSCEPTOMETER SOFTWARE 64
86
90
POSITION TRANSDUCER
VERTICAL MOTION DRIVE AND CONTROLLER
88
POSITION TRANSDUCER INTERFACE
MOTION CONTROLLER INTERFACE 92
58

FIG. 5

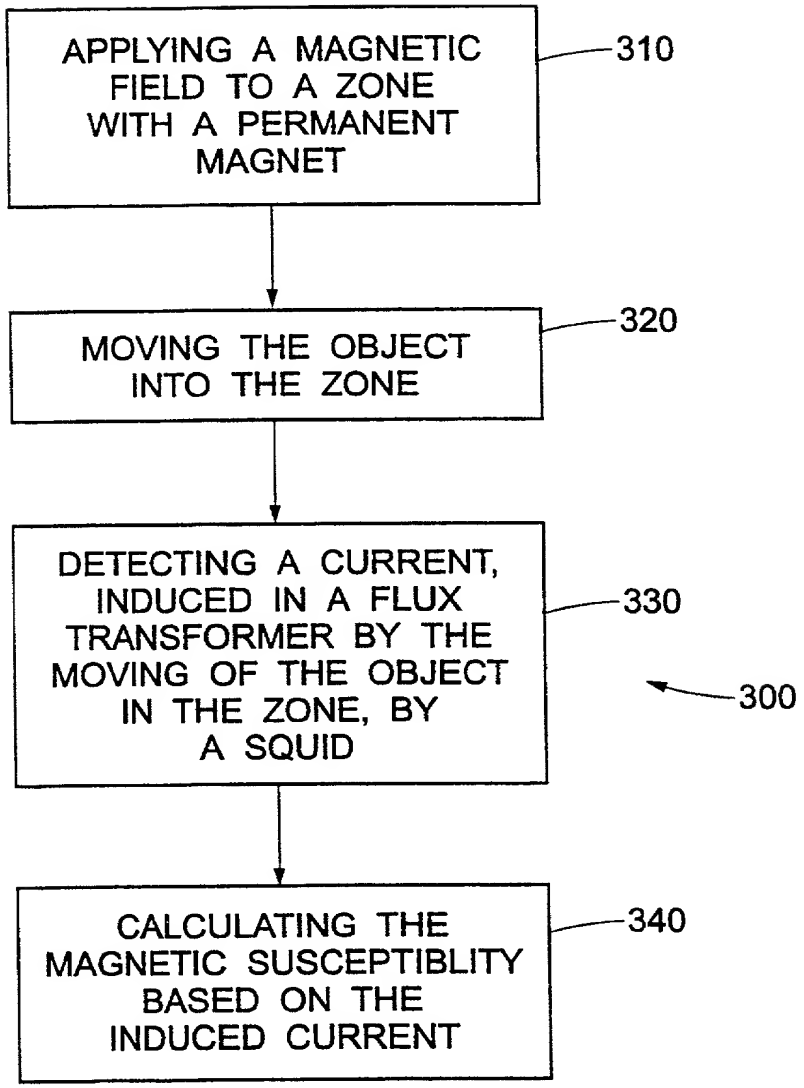

APPLYING A MAGNETIC FIELD TO A ZONE WITH A PERMANENT MAGNET
310
MOVING THE OBJECT INTO THE ZONE
320
DETECTING A CURRENT, INDUCED IN A FLUX TRANSFORMER BY THE MOVING OF THE OBJECT IN THE ZONE, BY A SQUID
330
300
CALCULATING THE MAGNETIC SUSCEPTIBLITY BASED ON THE INDUCED CURRENT
340

FIG. 6

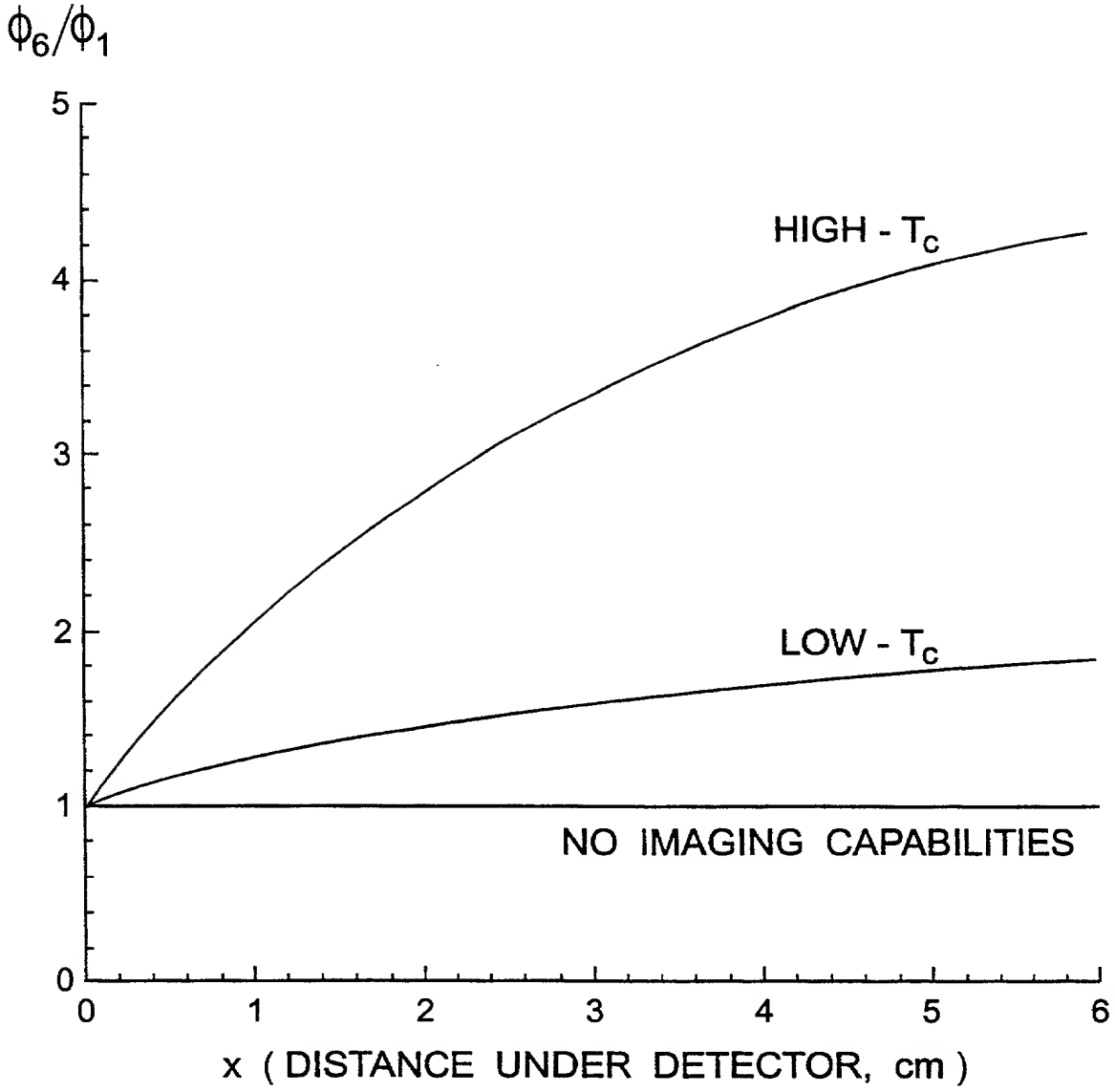
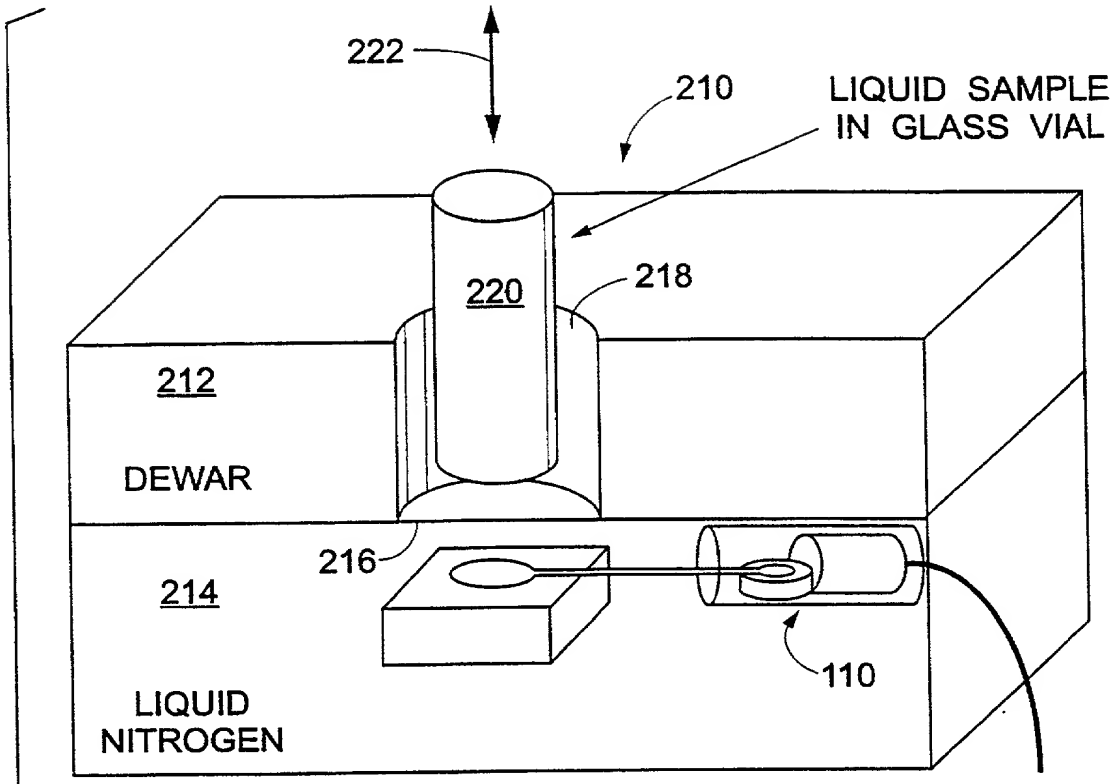
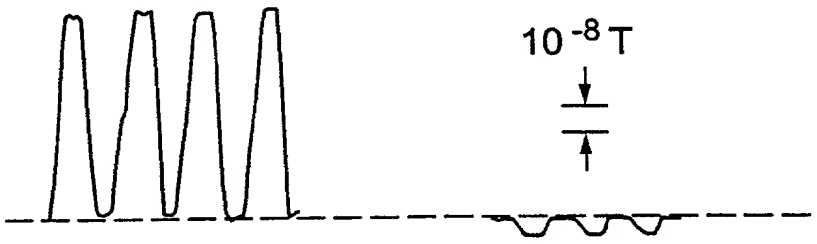

ϕ_6/ϕ_1
5
4
3
2
1
0
HIGH - T_c
LOW - T_c
NO IMAGING CAPABILITIES
0
1
2
3
4
5
6
x (DISTANCE UNDER DETECTOR, cm)

FIG. 7





FERROUS SULFATE SOLUTION

$X \sim +7 \times 10^{-5} SI$

WATER

$X \sim -9 \times 10^{-6} SI$

FIG. 8

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first, and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

APPARATUS AND METHOD FOR DETERMINING MAGNETIC SUSCEPTIBILITY

the specification of which:

☐ is attached hereto.
☒ was filed on February 21, 2001
as U.S. Serial No. 09/937,227

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PCT/US00/07829	United States	24 March 2000
(Number)	(Country)	(Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications listed below:

60/126,004	24 March 1999
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Serial No.)	(Filing Date)	(Status)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such

willful false statements may jeopardize the validity of the application or any patent issued thereon.

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